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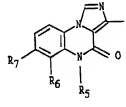
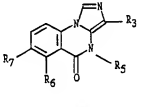


(I)



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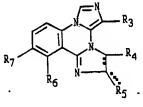

(III)

(a) —Aryl (b) —COAryl (c) —CSR$_{11}$ (d)

(57) Abstract

A 4-oxoimidazo(1,5-a)quinoxaline of formula (I), a 5-oxoimadazo(1,5-a)quinoxaline of formula (II), a diimidazoquinazoline of formula (III) or a pharmaceutically acceptable salt thereof, wherein R_3 is (a), (b), (c), (d). The R-groups and "Aryl" are as defined herein. The compounds are useful in the treatment of central nervous system disorders associated with the benzodiazepine receptors in a subject in need of such treatment comprising administering to the subject a therapeutically-effective amount of formula (I), (II) or (III) compound for alleviation of such disorder. Typically, the compound of formula (I), (II) or (III) is administered in the form of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier or diluent.

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3-substituted Imidazo (1,5-a)quinoxalines and quinazolines with CNS activity

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention is imidazo(1,5-a)quinoxalines and imidazo(1,5-a)quinazolines with aryl, heteroaryl, ketone and thioketone at position 3, which are uselful for treating anxiety, sleep disorders, panic disorders, convulsive disorders and/or depression.

2. Description of the Related Art

European Patent 225,013 (U.S. Patent 4,774,245; 4,771,051; 4,886,797; 4,880,799) disclose imidazo(1,5-a)quinoxaline and 4-oxoimidazo(1,5-a)quinoxalines compounds, useful as anxiolytic and hypnotic agents, having an ester or oxadiazole substituent at the 3-position.

European Patent 202,441-A discloses imidazo(1,5-a)quinazoline compounds useful as anxiolytic and hypnotic agents, containing an oxadiazole at the 3-position and halogen, nitrile, methyl and trifluoromethyl groups at the 6-position.

European Patent 320,136-A discloses 4-oxoimidazo(1,5-a)quinoxaline compounds useful as anxiolytic and hypnotic agents, containing oxadiazole or ester substituents at the 3-position and hydrogen or halogen substituents at the 6-position. The ring atom at position 6 may be carbon or nitrogen.

European Patent 283,162 (US 4,902,686; 4,873,244) discloses 4-oxoimidazo(1,5-a)quinoxalines and 5-oxoimidazo(1,5-a)quinazolines having anticonvulsant and anxiolytic activity, with oxadiazoles, esters, and amides at position 3.

European Patent 368,652 (US 4,999,353) discloses 4-oxoimidazoquinoxalines useful as anxiolytics and hypnotics with an oxadiazole at position 3 and tert-butyl at position 5.

European Patent Application 344,943A (US 5,075,304) discloses imidazo[1,5-a]quinoxalin-4-ones with methyl at N_5 useful as anticonvulsants, anxiolytics and hypnotics.

South African Patent 8701,535, assigned to The Upjohn Co., discloses 5-oxoimidazo(1,5-a)quinazolines having anxiolytic activity, with oxadiazole and ester substituents at position 3 and Cl at position 6.

Japanese Patent 89027074 discloses imidazobenzodiazepines useful as anticonvulsants and anxiolytics containing an oxadiazole at the 3-position.

U.S. Patent 4,440,929 discloses 4-thio, 4-imino, 4-hydroxyimino, 4-oxoimidazo(1,5-a)quinoxaline compounds containing nitrile, carboxaldehyde, carboxylic acid, ester, amide and methylalcohol substituents at the 3-position and H, alkyl, alkenyl, alkynyl, aryl, aralkyl, hydroxy, and alkanoyl at the 5-position.

U.S. Patent 4,866,065 discloses imidazo(1,5-a)thieno(2,3-e)pyrimidines useful as anticonvulsant, hypnotics, etc. containing oxadiazoles and esters at position 3.

U.S. Patent 5,034,530 discloses imidazo(1,5-a)quinoxalines useful as anxiolytics and

hypnotics with oxadiazoles at position 3 and no substitution at position 5 (imino) or 5 N-oxide.

U.S. Patent 4,939,139 discloses imidazo(1,5-a)benzodiazepines useful as anxiolytics containing an oxadiazole at position 3.

PCT Publication, WO 91/07407, (US 5,116,841) assigned to Ferrosan, discloses 4-oxoimidazoquinoxalines useful as anxiolytics and hypnotics with isoxazoles at position 3.

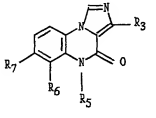
PCT Publication, WO 91/07408 discloses 4-oxoimidazoquinoxalines useful as anxiolytics and hypnotics with ketones at position 3.

J. Med. Chem (1991) 34, 281-290 discloses 5-oxo(1,2,4)triazolo(1,5-c)quinazolines with affinity for the benzodiazepine receptor, with phenyl, pyridinyl, CF_3, ester, furanyl, thienyl, tetrahydrofuranyl at position 2.

J. Med. Chem. (1988) 31 1098-1115 discloses 4-oxoimidazo(1,5-a)quinoxalines with an ester at position 3. The subject of the paper is antiallergy agents.

SUMMARY OF INVENTION

In one aspect the subject invention is directed toward 4-oxoimidazo(1,5-a)quinoxalines of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof,

wherein R_3 is

(a) —Aryl (b) —COAryl (c) —CSR_{11} (d)

("Aryl" is as defined and shown in Chart D, below and substituted with R_{14} and R_{15})

R_5 is C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, C_{2-6} alkenyl (optionally

substituted with C_{1-3} alkyl), $(CH_2)_n$-Aryl, $(CH_2)_mN(R_{12})_2$, or $(CH_2)_mOR_{11}$ and n is 0-4 and m is 2-4;

R_6 and R_7 are independently H, F, Cl, Br, I, C_1-C_4 alkyl, C≡N, NO_2, CF_3, $(CH_2)_nOR_{11}$, CO_2R_{11}, $CON(R_{12})_2$, $(CH_2)_nN(R_{12})_2$, $(OCH_2CH_2)_n$-OH or $NHCOR_{11}$;

R_8 is O, S, NH, NCH_3, $N(CH_2)_n$-C_{3-7} cycloalkyl, $-C(R_9)_2$ or NCHO;

R_9 is H, C_{1-4} alkyl, phenyl (except that only one R_9 can be phenyl or t-butyl at the same time);

R_{11} is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, or $-(CH_2)_n$-Aryl;

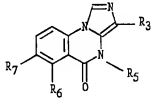
R_{12} is independently H, C_{1-6} alkyl, C_3-C_7 cycloalkyl, -C_{1-4} alkyl-C_{3-7} cycloalkyl, phenyl, or taken together with the attached nitrogen atom to form a heterocyclic ring - $N^*(CH_2)_pR_{13}(CH_2)_o$* where the * indicates the atoms bonded to each other to form said heterocyclic ring, where p is 2-5 and o is 0-3;

R_{13} is O, S, CO, CH_2, NR_{16};

R_{14} is independently H, F, Cl, Br, I, CN, NO_2, $OCOR_{11}$, $(CH_2)_nCF_3$, C_{1-6} alkyl, C_3-C_7 cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, $(CH_2)_nN(R_{12})_2$, $(CH_2)_nOR_{11}$, $N(R_{12})COR_{11}$, $(CH_2)_nCO_2R_{11}$, $(CH_2)_nSR_{11}$, $SO_2N(R_{12})_2$, COR_{11}, phenyl (optionally substituted with F, Cl, Br, OCH_3, CH_3 or CF_3); and

R_{16} is H, C_{1-4} alkyl, C_3-C_7 cycloalkyl, CHO, C_{1-4} alkyl-C_{3-7} cycloalkyl, CO-R_{11}.

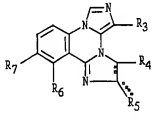
In another aspect the subject invention is directed toward 5-oxoimidazo(1,5-a)quinazoline of formula (II)



(II)

The R-groups are as defined above.

In yet another aspect the subject invention is directed toward a diimidazoquinazoline of formula (III)



(III)

or a pharmaceutically acceptable salt thereof. where R_4 is a H or C_{1-6} alkyl; and the remaining

R-groups are as defined above except that R_5 includes a H.

The preferred compounds of the 4-oxoimidazo(1,5-a)quinoxaline (I) are where R_3 is selected from the group consisting of benzoxazol-2-yl, oxazolin-2-yl, thiazol-2-yl, 1,2,4-triazol-3-yl and a phenyl optionally substituted with one $-CH_3$, $-OCH_3$ or -F. More preferred is where R_3 is selected from the group consisting of 4-fluorophenyl, thiazol-2-yl and benzoxazol-2-yl. For the 4-oxoimidazo(1,5-a)quinoxaline (I) compounds, R_5 is preferably a C_1-C_4 alkyl and R_6 and R_7 are independently -H, -F, -Cl, $-CF_3$ or $-CH_3$. The preferred compounds of 4-oxoimidazo(1,5-a)quinoxaline (I) are exemplified in Examples 1-16.

The preferred compounds of the 5-oxoimidazo(1,5-a)quinazoline (II) are where R_3 is selected from the group consisting of substituted phenyl, benzoxazol-2-yl, thiazol-2-yl, oxazolin-2-yl and 1,2,4-triazol-3-yl, more preferably where R_3 is selected from the group consisting of 4-fluorophenyl, thiazol-2-yl and benzoxazol-2-yl. Preferably, R_5 is a C_{1-4} alkyl and R_6 and R_7 are independently -H, -F, -Cl, $-CF_3$ or $-CH_3$.

The preferred compounds of the diimidazoquinazoline (III) are where R_3 is selected from the group consisting of substituted phenyl, thiazol-3-yl, benzoxazol-2-yl, oxazolin-2-yl and 1,2,4-triazol-3-yl, more preferably where, R_3 is selected from the group consisting of 4-fluorophenyl, thiazol-2-yl and benzoxazol-2-yl. Preferably, R_5 is a C_1-C_4 alkyl and R_6 and R_7 are independently -H, -F, -Cl, $-CF_3$ or $-CH_3$.

In another aspect, the subject invention is directed toward a method for treating central nervous system disorders associated with benzodiazepine receptors in a subject or patient in need of such treatment comprising administering to the patient a therapeutically-effective amount of a Formula I, II or III compound for alleviation of such disorder. Typically, the compound of Formula I, II or III is administered in the form of a pharmaceutical composition comprising a pharmaceutically-acceptable carrier or diluent.

In yet another aspect, the subject invention is directed toward a pharmaceutical composition for treating central nervous system disorders associated with the benzodiazepine receptors comprising an effective amount of a compound of Formula I, II, or III with a pharmaceutically-acceptable carrier or diluent.

DETAILED DESCRIPTION OF THE INVENTION

The 4-oxoimidazo(1,5-a)quinoxalines (I) of the present invention are named and numbered following the Chemical Abstracts ring system nomenclature system, see Ring Systems Handbook, Chemical Abstracts Service, Ring Systems File I, see RF 23543, 1988 Edition.

The 4-oxoimidazo(1,5-a)quinoxalines (I) are prepared as set forth in CHART A by methods well known to those skilled in the art, see US Patent 4,774,245. The diketoquinoxalines (V) are reacted with the appropriate isocyanides (VI) to form the 4-

oxoimidazo(1,5-a)quinoxalines (I).

The diketoquinoxalines (V) are known to those skilled in the art or can be readily prepared by known means from known compounds, see for example, US Patent 4,774,245.

The isocyanides (VI) are either known to those skilled in the art or can be readily be prepared by known methods from compounds known to those skilled in the art. A general review of synthesis of isocyanides (also known as isonitriles) is found in Angew. Chem. Internat. Edit., 4, 472 (1963). One method involves starting with primary amines of the formula NH_2-CH_2-R_3, which are known to those skilled in the art. These primary amines are then reacted with a reagent such as methyl or ethylformate (or their equivalent) by known means at about 20-25° to provide the corresponding formamide, CHO-NH-CH_2-R_3. The formamides are then transformed to the isocyanides (VI) by exposure to phosphorous oxychloride in a solvent such as methylene chloride in the presence of a base such as triethylamine by known means (preferred for higher molecular weight isocyanides). For low molecular weight isocyanides, the method of J. Chem. Soc. (Lon.) 4280 (1963), using p-toluenesulfonyl chloride and quinoline is useful. Alternatively, the isocyanides (VI) can be prepared directly from the primary amine by treatment with chloroform and a base, see Tetrahedron Letters, 1637 (1972) or Angew. Chem. Int. Ed. Engl., 11, 530 (1972). Alternatively, when the desired primary amine containing R_3 is not available one can start with a primary amine of the formula NH_2-CH_2-X_3 where X_3 may contain an amino or hydroxy group which may require protection. This may be accomplished with standard protecting groups such as acetate, benzyl, tert-butyl, and tert-butyloxycarbonyl. The protecting group may be removed by standard procedures at the completion of the isocyanide synthesis, or at the completion of the synthesis of the final product 4-oxoimidazo(1,5-a)quinoxalines (I). These amines are then formylated to give the CHO-NH-CH_2-X_3 as discussed above. The formyl amines are then converted to isocyanides (CN-CH_2-X_3), as discussed above. For other isocyanides, the synthesis may begin with halo-CH_2-R_3 or HO-CH_2-R_3 (which itself may be converted to halo-CH_2-R_3 or the hydroxy group may be converted to a leaving group such as p-toluenesulfonate or methanesulfonate), which are then converted to NH_2-CH_2-R_3 by standard routes such as displacement with azide and reduction of azide to amine. The NH_2-CH_2-R_3 are then converted to the isocyanides (VI) using the procedures mentioned above. Further, the halo group of halo-CH_2-R_3 may be directly displaced with the anion formed from formamide and a strong base such as sodium hydride to produce directly the CHO-NH-CH_2-R_3 precursor to the isocyanides (VI). In some cases halo-CH_2-R_3 or HO-CH_2-R_3 are not commercially available and must be prepared. This can be accomplished using several methods. One method begins with 2-halo acetyl halide, which is reacted with o-hydroxy, o-thiol, or o-aminoanilines (aryl or heteroaryl) to form an amide or ester. In some cases it may be preferable to protect either the anilino group or the o-hydroxy, thiol, or amino group during the

addition to the acid halide. When the addition is complete, the protecting group is removed and the resulting amide or ester is subjected to dehydrating and cyclizing conditions such as methanesulfonic acid saturated with phosphorous pentoxide. This then gives the desired halo-CH_2-R_3, which are then taken on to the isocyanides (VI) by the procedures mentioned above. Still another method is to add 2-haloacetyl halide to an ortho-halo aniline using refluxing trimethyl polyphosphate, a variation of the method of EP 419 348. For both of these methods, protection of groups on the aryl or heteroaryl portion of R_3 is through standard methods such as acetate, tert-butyl, tert-butyloxycarbonyl, benzyl, and others.

The desired diketoquinoxalines (V) are contacted with the isocyanides (VI) to produce the desired 4-oxoimidazo(1,5-a)quinoxalines (I) as is known in the art. More particularly, the diketoquinoxalines (V) are cooled and contacted with a small excess of strong base, preferably potassium tert-butoxide or its equivalent. After stirring, diethyl chlorophosphate is added. After further stirring, isocyanide (VI) is added with potassium tert-butoxide. After stirring for 1-4 hours the mixture is allowed to return to ambient temperature. The mixture is then partitioned between the ethyl acetate or methylene chloride and aqueous sodium bicarbonate or water and purified.

In some cases it may be preferable to attach an appropriate amine to an already constructed 3-substituted-4-oxoimidazo(1,5-a)quinoxaline or imidazoquinoxaline-carboxylate (IX), produced from reaction of diketoquinoxalines (V) with isocyanides (XII), to form an amide (IX), which is then cyclized with loss of water or with loss of some leaving group such as halo or mesylate or tosylate to form the desired 4-oxoimidazo(1,5-a)quinoxalines (I). Additional routes to the construction of R3 groups are given in J. Med. Chem. 34, 2060 (1991), which details the construction of imidazo(1,2-a)pyrimidine acids, amides, aldehydes, alcohols, nitriles, triazoles, oxadiazoles, thioamides, thiazoles, oxazoles, thiadiazoles, hydrazides and pyrrazoles. Another method, to form a 5-substituted oxazole, is that of Angew. Chem. Internat. Edit., 10, 333 (1971).

The 5-oxoimidazo(1,5-a)quinazolines (II) are prepared as set forth in CHART B by known means, see J8 9027 074B and US Patent 4,774,245. The dioxoquinazolines (VII) starting materials are known to those skilled in the art and are reacted with the isocyanides (VI) as discussed above. Alternatively, the R_3 group may be added following formation of an X_3 substituted-5-oxoimidazo(1,5-a)quinazoline (X), more particularly an imidazoquinazoline-carboxylate (X) as discussed above. In those cases the 3-substituted-5-oxoimidazo(1,5-a)quinazolines (X) are then converted to 5-oxoimidazo(1,5-a)quinazolines (II) by known means.

The diimidazoquinazolines (III) are prepared as set forth in CHART C by known means, see European Patent Application No. EP 417027A1 assigned to Ferrosan. The tricyclic amide (VIII) starting materials are known to those skilled in the art and are reacted with the

isocyanides (VI) as discussed above. Alternatively, the R_3 group may be added following formation of a X_3 substituted-diimidazoquinazolines (XI), more particularly an imidazoquinoxaline-carboxylate (XI) as discussed above. In those cases the X_3 substituted-diimidazoquinazolines (XI) are then converted to diimidazoquinazolines (III) by known means.

In Formulas I, II and III, it is preferred that R_3 be benzoxazol-2-yl, oxazolin-2-yl, thiazol-2-yl, 1,2,4-triazol-3-yl and phenyl optionally substituted with a $-CH_3$, $-OCH_3$ or -F; it is more preferred that R_3 be 4-fluorophenyl, thiazol-2-yl or benzoxazol-2-yl. It is preferred that R_5 be C_{1-4}alkyl; it is more preferred that R_5 be C_3 alkyl and it is even more preferred that R_5 be isopropyl. It is preferred that R_6 and R_7 are H, F, Cl, CF_3 or CH_3, more preferrably that R_6 is -H, $-CH_3$ or -Cl and more preferrably that R_7 is -H, -Cl or -F. It is preferred that the 4-oxoimidazo(1,5-a)quinoxalines (I) be the compounds of EXAMPLES 1-12.

It is also preferred that R_3 is an aryl such as phenyl, included substituted phenyls, Aryl-I to III (shown in Chart D) and heteroaryls Aryl-IV through Aryl-LXIV (shown in Chart D).

For convenience the 4-oxoimidazo(1,5-a)quinoxalines (I), 5-oxoimidazo(1,5-a)quinazolines (II) and the diimidazoquinazolines (III) all will be referred to as imidazo(1,5-a)quinoxalines (IV).

The imidazo(1,5-a)quinoxalines (IV) are amines, and as such may form acid addition salts when reacted with acids of sufficient strength. Pharmaceutically acceptable salts include salts of both inorganic and organic acids. The pharmaceutically acceptable salts are preferred over the corresponding free amines since they produce compounds which are more water soluble and more crystalline. The preferred pharmaceutically acceptable salts include salts of the following acids methanesulfonic, hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric, maleic, CH_3-$(CH_2)_n$-COOH where n is 0 thru 4, HOOC-(CH_2)n-COOH where n is as defined above.

The imidazo(1,5-a)quinoxalines (IV) of the present invention have relatively more anxiolytic and less sedative activity than other known anxiolytic compounds such as diazepam and therefore are useful as anxiolytic agents at lower doses and as sedatives at higher doses.

The imidazo(1,5-a)quinoxalines (IV) are active orally or parenterally. Orally the imidazo(1,5-a)quinoxalines (IV) can be given in solid dosage forms as tablets or capsules, or can be given in liquid dosage forms such as elixirs, syrups or suspensions as is known to those skilled in the art. It is preferred that the 4-oxoimidazo(1,5-a)quinoxalines (IV) be given in solid dosage form and that it be a tablet or capsule.

For anxiolytic effect the imidazo(1,5-a)quinoxalines (IV) should be administered in a therapeutically effective amount to a subject or patient in an amount of about 0.25 mg to about 100 mg/person, one to three times a day. Preferably, about 1 to about 50 mg/day in divided doses.

For sedative/hypnotic effect the imidazo(1,5-a)quinoxalines (IV) should be administered in a therapeutically effective amount to a subject or patient in an amount of about 0.25 mg to about 100 mg/person, preferrably at bedtime or when sedation is needed. It is preferred the sedative/hypnotic dose be from about 1 to about 50 mg/person.

For treating panic disorders the imidazo(1,5-a)quinoxalines (IV) should be administered in a therapeutically effective amount to a subject or patient in an amount of about 1 mg to about 100 mg/person. It is preferred the dose be from about 1 to about 50 mg/person.

For treating/preventing convulsions the imidazo(1,5-a)quinoxalines (IV) should be administered in a therapeutically effective amount to a subject or patient in an amount of about 1 mg to about 100 mg/person. It is preferred the anti-convulsive dose be from about 1 to about 50 mg/person.

For treating depression the imidazo(1,5-a)quinoxalines (IV) should be be administered in a therapeutically effective amount to a subject or patient in an amount of about 1 mg to about 100 mg/person. It is preferred the anti-depressant dose be from about 1 to about 50 mg/person.

The exact dosage and frequency of administration depends on the particular imidazo(1,5-a)quinoxalines (IV) used, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the imidazo(1,5-a)quinoxalines (IV) in the patient's blood and/or the patient's response to the particular condition being treated.

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical subscript, for example, "R_i" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the formula by one or two chemical bonds. For example, a group R_1 would represent a bivalent variable if attached to the formula CH_3-C(=R_1)H. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula CH_3-CH_2-C(R_i)(R_j)-H. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both R_i and R_j are bonded to the preceding

carbon atom. Also, for any molecule with an established system of carbon atom numbering, such as steroids, these carbon atoms are designated as C_i, where "i" is the integer corresponding to the carbon atom number. For example, C_6 represents the 6 position or carbon atom number in the steroid nucleus as traditionally designated by those skilled in the art of steroid chemistry. Likewise the term "R_6" represents a variable substituent (either monovalent or bivalent) at the C_6 position.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus CH_3-O-CH_2-CH(R_i)-CH_3 represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., CH_2=C(R_i)-O-CH_3, and the symbol "≡" represents a triple bond, e.g., HC≡C-CH(R_i)-CH_2-CH_3. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

The carbon atom content of variable substituents is indicated in one of two ways. The forms are either "C_{i-k}" or "C_i-C_k" where both "i" and "k" are integers representing the minimum and maximum number of carbon atoms in the variable. For example, "C_1-C_4 alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus C_2-C_4 alkoxycarbonyl describes a group CH_3-$(CH_2)_n$-O-CO- where n is zero, one or two. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the "C_i-C_j" designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention (C_1-C_3)alkoxycarbonyl has the same meaning as C_2-C_4 alkoxycarbonyl because the "C_1-C_3" refers only to the carbon atom content of the alkoxy group. Similarly while both C_2-C_6 alkoxyalkyl and (C_1-C_3)alkoxy(C_1-C_3)alkyl define alkoxyalkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

"Aryl" is defined as those compounds (structures) shown in Chart D.

Chart D shows the compounds identified by the "Aryl Roman numeral" designation as all of which can be optionally substituted with the R_{14} or R_{16} group as defined above.

phenyl	(Aryl I)	3-pyridyl	(Aryl V)
1-naphthyl	(Aryl II)	4-pyridyl	(Aryl VI)
2-naphthyl	(Aryl III)	2-pyrimidinyl	(Aryl VII)
2-pyridyl	(Aryl IV)	4-pyrimidinyl	(Aryl VIII)

	5-pyrimidinyl	(Aryl IX)	3-pyrrolyl	(Aryl XLV)
	3-pyridazinyl	(Aryl X)	1,2,4-triazol-3-yl	(Aryl XLVI)
	4-pyridazinyl	(Aryl XI)	1,2,4-triazol-5-yl	(Aryl XLVII)
	2-pyrazinyl	(Aryl XII)	5-oxazolyl	(Aryl XLVIII)
5	2-quinolyl	(Aryl XIII)	5-thiazolyl	(Aryl XLIX)
	3-quinolyl	(Aryl XIV)	1-imidazolyl	(Aryl L)
	4-quinolyl	(Aryl XV)	1-pyrrolyl	(Aryl LI)
	1-isoquinolyl	(Aryl XVI)	1-pyrazolyl	(Aryl LII)
	3-isoquinolyl	(Aryl XVII)	1,2,4-triazol-1-yl	(Aryl LIII)
10	4-isoquinolyl	(Aryl XVIII)	1,2,3,4-tetrazol-1-yl	(Aryl LIV)
	2-quinazolinyl	(Aryl XIX)	1-indolyl	(Aryl LV)
	4-quinazolinyl	(Aryl XX)	1-indazolyl	(Aryl LVI)
	2-quinoxalinyl	(Aryl XXI)	2-isoindolyl	(Aryl LVII)
	1-phthalazinyl	(Aryl XXII)	1-purinyl	(Aryl LVIII)
15	2-imidazolyl	(Aryl XXIII)	3-isothiazolyl	(Aryl LIX)
	4-imidazolyl	(Aryl XXIV)	4-isothiazolyl	(Aryl LX)
	3-pyrazolyl	(Aryl XXV)	5-isothiazolyl	(Aryl LXI)
	4-pyrazolyl	(Aryl XXVI)	oxazolo(4,5-b)pyridin-2-yl	(Aryl-LXII)
	5-pyrazolyl	(Aryl XXVII)	1,2,3-triazol-4-yl	(Aryl-LXIII)
20	2-oxazolyl	(Aryl XXVIII)	1,2,4-triazol-3-yl	(Aryl-LXIV)
	4-oxazolyl	(Aryl XXIX)		
	2-thiazolyl	(Aryl XXX)		
	4-thiazolyl	(Aryl XXXI)		
	2-indolyl	(Aryl XXXII)		
25	3-indolyl	(Aryl XXXIII)		
	3-indazolyl	(Aryl XXXIV)		
	2-benzoxazolyl	(Aryl XXXV)		
	2-benzothiazolyl	(Aryl XXXVI)		
	2-benzimidazol	(Aryl XXXVII)		
30	2-benzofuranyl	(Aryl XXXVIII)		
	3-benzofuranyl	(Aryl XXXIX)		
	2-furanyl	(Aryl XL)		
	3-furanyl	(Aryl XLI)		
	2-thienyl	(Aryl XLII)		
35	3-thienyl	(Aryl XLIII)		
	2-pyrrolyl	(Aryl XLIV)		

Other definitions are used as follows: All temperatures are in degrees Centigrade. THF refers to tetrahydrofuran, DMF is dimethylformamide, DMSO is dimethylsulfoxide and $CDCl_3$ is deuteriochloroform. Saline refers to an aqueous saturated sodium chloride solution. IR refers to infrared spectroscopy. NMR refers to nuclear (proton) magnetic resonance spectroscopy, chemical shifts are reported in ppm (δ) downfield from tetramethylsilane. MS refers to mass spectrometry expressed as m/e or m/z. $(M + H)^+$ refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment. Ether refers to diethyl ether. Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/-toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability. When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

PREPARATION 1 2-Chloro-N-(2-hydroxyphenyl)acetamide

To a mixture of 8.90 g of 2-aminophenol, 11.4 ml of triethylamine, and 250 ml of ethyl acetate cooled at 0° are added dropwise over several minutes 6.5 ml of chloroacetyl chloride. After 80 min the mixture is partitioned between ethyl acetate, saline, and aqueous sodium bicarbonate and saline. The organic layers are dried over magnesium sulfate and concentrated. Dichloromethane is added to the residue and the solid is collected and dried to give the title compound, mp 133-134°; NMR ($CDCl_3$) 4.27, 6.93, 7.02, 7.17, 7.25, 7.80 and 8.53 δ.

PREPARATION 2 2-(Chloromethyl)benzoxazole

A mixture of 2-chloro-N-(2-hydroxyphenyl)acetamide (PREPARATION 1, 14.55 g) and approximately 35 ml of a solution prepared by stirring overnight methanesulfonic acid and phosphorous pentoxide in a 10/1 (wt/wt) ratio is heated with stirring at 100° for 2 hours and then poured onto ice. The aqueous mixture is extracted with dichloromethane. The dichloromethane layers are washed with aqueous sodium bicarbonate and the organic layers dried over sodium sulfate. After concentration, the crude product is chromatographed on silica gel (600 ml) eluting with dichloromethane. The appropriate fractions are pooled and

concentrated to give the title compound, NMR ($CDCl_3$) 4.77, 7.40, 7.57 and 7.75 δ.

PREPARATION 3 2-(Azidomethyl)benzoxazole

To a mixture of 2-(chloromethyl)benzoxazole (PREPARATION 2, 8.34 g) and sodium iodide (0.75 g) in DMSO (25 ml) is added sodium azide (3.56 g). A moderate exotherm ensued. After stirring for 30 min the reaction is partitioned between ether and saline. The organic layers are dried over magnesium sulfate and concentrated. The crude product is chromatographed on silica gel (700 ml) eluting with ethyl acetate/hexane (5/95). The appropriate fractions are pooled and concentrated to give the title compound, NMR ($CDCl_3$) 4.60, 7.39, 7.56 and 7.76 δ.

PREPARATION 4 2-(Aminomethyl)benzoxazole

A mixture of 2-(azidomethyl)benzoxazole (PREPARATION 3, 8.28 g) and 0.526 g of 10% palladium on charcoal in 150 ml of absolute ethanol is shaken under hydrogen at 36 psi for 40 min. The catalyst is then filtered off and the filtrate is concentrated. The crude product is chromatographed on silica gel (700 ml) eluting with methanol/dichloromethane (2/98). The appropriate fractions are pooled and concentrated to give the title compound. Crystallization is from ether/hexane, mp 46.5-47.5 °C; MS (m/z) at 148; NMR ($CDCl_3$) 1.70, 4.14, 7.33, 7.51, 7.70 δ.

PREPARATION 5 2-(N-Formylaminomethyl)benzoxazole

A mixture of 2-(aminomethyl)benzoxazole (PREPARATION 4, 4.29 g) and 20 ml of ethyl formate is heated at 80° for 2 hr, after which the excess ethyl formate is removed under reduced pressure. The residue is chromatographed on silica gel (350 ml) eluting with methanol/dichloromethane (2/98), pooling and concentrating the appropriate fractions to give the title compound, which is crystallized from dichloromethane/hexane, mp 98-99°; MS (m/z) at 176; IR (mineral oil) 1655, 1621, 1519, 1241, 750 cm^{-1}; NMR ($CDCl_3$) 4.81, 6.45, 7.36, 7.53, 7.70, 8.39 δ.

PREPARATION 6 2-(Isocyanomethyl)benzoxazole (VI)

To 2-(N-formylaminomethyl)benzoxazole (PREPARATION 5, 2.83 g), 7.39 ml of triethylamine, and 30 ml of dichloromethane stirred at 0° are added dropwise 2.71 g of phosphorous oxychloride in dichloromethane (5 ml). The reaction mixture is stirred at 0° for 45 min and then 2.81 g of sodium carbonate dissolved in 20 ml of water is added. The mixture is stirred for 30 min and then partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layers are dried over sodium sulfate and concentrated and the crude product is chromatographed on silica gel (325 ml) eluting with ethyl acetate/hexane (10/90), pooling and concentrating the appropriate fractions to obtain the title compound, mp 57.0-57.5°; MS (m/z) at 158; IR (mineral oil) 766, 2166. 987, 1167, 1230 cm^{-1}; NMR ($CDCl_3$) 4.94, 7.42, 7.58, 7.76 δ.

EXAMPLE 1 4,5-Dihydro-5-isopropyl-3-(4-methoxyphenyl)-4-oxoimidazo(1.5-a)quinoxaline (I)

Potassium tert-butoxide (1M in THF, 8.10 ml) is added dropwise over 10 min to a mixture of 1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 1.50 g), THF (5.5 ml) and DMF (1.5 ml) at 0°. The mixture is allowed to warm to 20-25° and is stirred for 10 min. After cooling to -25°, diethyl chlorophosphate (1.38 ml) is added. The mixture is stirred 15 min at -25° and is allowed to warm to 20-25°. After 15 min the resultant solution is cooled to -25°. A solution of 4-methoxybenzyl isocyanide (VI, 1.19 g) and THF (2.0 ml) is added dropwise over 2 min and the solution allowed to stir for 5 min. Additional potassium tert-butoxide (8.10 ml) is added dropwise over 10 min. The solution is allowed to warm to 20-25° over 2 hr and is quenched with acetic acid (1.0 ml). Aqueous workup (methylene chloride and sodium sulfate) followed by flash chromatography eluting with acetone/methylene chloride (9/91) and pooling/concentrating the appropriate fractions gives the title compound. An analytical sample is obtained via recrystallization from methylene chloride/hexane, mp 187-189°; IR (mineral oil) 2924, 1654, 1503, 1296, 1247, 1175, 743 cm^{-1}; NMR ($CDCl_3$) 8.43, 8.17, 7.79, 7.53, 7.3-7.45, 7.2-7.3, 7.00, 5.25-5.5, 3.86, 1.66 δ; MS (EI) m/e 333, 318, 291, 276.

EXAMPLE 2 7-Fluoro-4,5-dihydro-5-isopropyl-4-oxo-3-phenylimidazo(1,5-a)quinoxaline (I)

Potassium tert-butoxide (1.0 M in THF, 4.50 ml) is added to a solution of the 7-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 1.00 g), and THF (7.1 ml) at -20°. The solution is allowed to warm to 0° over 50 min. After cooling to -40°, diethyl chlorophosphate (0.67 ml) is added. The solution is allowed to warm to 0° over 70 min. After cooling to -78°, benzyl isocyanide (VI, 0.60 ml) and potassium tert-butoxide (4.50 ml) are added successively. The reddish solution is stirred at -78° for 30 min and is allowed to warm slowly to 20-25°. After 16 hr, aqueous workup (ethyl acetate, magnesium sulfate), purification by flash chromatography eluting with methylene chloride/acetone: 20/1 → 8/1 and pooling/concentrating the appropriate fractions gives the title compound. An analytical sample is prepared by recrystallization from ethyl acetate/hexane, mp 223-224°; IR (mineral oil) 3094, 2955, 2925, 2855, 1657, 1598, 1520, 1361, 1291, 1218, 1095, 752 cm^{-1}; NMR ($CDCl_3$) 8.40, 8.16, 7.77, 7.3-7.5, 7.2-7.3, 6.9-7.0, 5.1-5.5, 1.66 δ; MS (EI) m/e 321, 279.

EXAMPLE 3 3-(4-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline (I)

A solution of the 1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 1.00 g) in THF (15 ml) is cooled to -30° and potassium tert-butoxide (1.0 M in THF, 5.90 ml) is added dropwise over 2 min. The mixture is allowed to warm to 20-25° over 30 min and is cooled to -40°. Diethyl chlorophosphate (0.92 ml) is added and the mixture is allowed to warm to 20-25° over 30 min. The solution is cooled to -78° and 4-fluorobenzyl isocyanide (VI, 794 mg) is added. Potassium tert-butoxide (5.90 ml) is added dropwise over 5 min. The solution is

allowed to warm slowly and is stirred at 20-25° for 19 hr. After quenching with water, aqueous workup (ethyl acetate, magnesium sulfate), flash chromatography ethyl acetate/hexane (40 → 75/60 → 25), and recrystallization from ethyl acetate/hexane gives the title compound, mp 201-202°; IR (mineral oil) 2925, 2855, 1653, 1503, 1299, 1219, 1161, 746 cm^{-1}; NMR ($CDCl_3$) 8.45, 8.15-8.25, 7.81, 7.56, 7.40, 7.2-7.3, 7.1-7.2, 5.38, 1.67 δ; MS (EI) m/e 321, 306, 279, 251, 223.

EXAMPLE 4 7-Fluoro-3-(4-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline (I)

Following the the general procedure of EXAMPLES 1-3 and making non-critical variations but using 7-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 1.50 g) and 4-fluorobenzyl isocyanide (VI, 1.09 g) the title compound is obtained, mp 229-230°; IR (mineral oil) 2954, 2925, 1663, 1505, 1298, 1290, 1221, 1161 cm^{-1}; NMR ($CDCl_3$) 8.39, 8.15-8.25, 7.77, 7.2-7.3, 7.15, 6.95-7.05, 5.30, 1.66 δ; MS (EI) m/e 339, 297.

EXAMPLE 5 6-Chloro-3-(4-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline (I)

Following the the general procedure of EXAMPLES 1-3 and making non-critical variations but using 8-chloro-1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 931 mg) and 4-fluorobenzyl isocyanide (VI, 632 mg) the title compound is obtained, mp 157-158°; IR (mineral oil) 2954, 2926, 1667, 1504, 1462, 1289, 1246, 1158, 840, 766 cm^{-1}; NMR ($CDCl_3$) 8.36, 8.15-8.25, 7.63, 7.43, 7.1-7.25, 4.55-4.7, 1.68 δ; MS (EI) m/e 355, 313.

EXAMPLE 6 4,5-Dihydro-5-isopropyl-4-oxo-3-phenylimidazo(1,5-a)quinoxaline (I)

Following the the general procedure of EXAMPLES 1-3 and making non-critical variations but using 1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 1.00 g) and benzyl isocyanide (VI, 0.77 ml), the title compound is obtained, mp 207-208°; IR (mineral oil) 3089, 2955, 2925, 2855, 1662, 1656, 1515, 1501, 1478, 1304, 1298, 1221, 745, 692 cm^{-1}; NMR ($CDCl_3$) 8.46, 8.17, 7.80, 7.54, 7.15-7.5, 5.2-5.6, 1.65 δ; MS (EI) m/e 303, 261.

EXAMPLE 7 3-(2-Furyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline (I)

Following the the general procedure of EXAMPLES 1-3 and making non-critical variations but using 1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 1.00 g) and 2-furfuryl isocyanide (VI, 0.679 g), the title compound is obtained, mp 242-243°; IR (mineral oil) 3083, 2955, 2920, 2855, 1662, 1514, 1462, 1381, 1299, 1284, 1029, 745, 739 cm^{-1}; NMR ($CDCl_3$) 8.43, 7.7-7.85, 7.58, 7.55, 7.40, 7.2-7.3, 6.57, 5.3-5.5, 1.68 δ; MS (EI) m/e 293, 251.

EXAMPLE 8 4,5-Dihydro-5-isopropyl-3-(4-methylphenyl)-4-oxoimidazo(1,5-a)quinoxaline (I)

Following the the general procedure of EXAMPLES 1-3 and making non-critical variations but using 1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 2.33 g) and 4-methylbenzyl isocyanide (VI), the title compound is obtained, mp 209-210°; IR (mineral oil) 2925, 1662, 1504, 1304, 1296, 742 cm^{-1}; NMR ($CDCl_3$) 8.44, 8.06, 7.79, 7.53, 7.3-7.4, 7.2-7.3,

5.25-5.5, 2.39, 1.65 δ; MS (EI) m/e 317, 302, 275, 247, 219.

EXAMPLE 9 3-(Benzoxazol-2-yl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline (I)

Following the the general procedure of EXAMPLES 1-3 and making non-critical variations but using 1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 0.693 g) and 2-(isocyanomethyl)benzoxazole (VI, PREPARATION 6, 0.644 g), the title compound is obtained, mp 284-285°; MS (m/z) at 344; IR (mineral oil) 743, 1679, 1450, 1308, 1315 cm^{-1}; NMR ($CDCl_3$) 1.70, 5.65, 7.30-7.41, 7.47, 7.68, 7.91, 8.59 δ.

EXAMPLE 10 3-(Benzoxazol-2-yl)-7-fluoro-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline (I)

Following the the general procedure of EXAMPLES 1-3 and making non-critical variations but using 7-fluoro-1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 0.511 g) and 2-(isocyanomethyl)benzoxazole (VI, PREPARATION 6, 0.400 g) the title compound is obtained, mp >310°; MS (m/z) at 362; IR (mineral oil) 1687, 1045, 750, 1451, 1491 cm^{-1}; NMR (DMSO) 1.57, 7.31, 7.48, 7.70, 7.83, 8.41, 9.27 δ.

EXAMPLE 11 4,5-Dihydro-5-isopropyl-3-(oxazolin-2-yl)-4-oxoimidazo(1,5-a)quinoxaline (I)

Following the the general procedure of EXAMPLES 1-3 and making non-critical variations but using 1,2,3,4-tetrahydro-1-isopropyl-2,3-dioxoquinoxaline (V, 1.108 g) and tert-butyl isocyanoacetate (XII, 0.918 g) are converted to tert-butyl 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxylate (IX). After crystallization from dichloromethane/hexane, mp 155-156°; MS (m/z) at 327; IR (mineral oil) 1734, 1683, 1288, 1342, 1160 cm^{-1}; NMR ($CDCl_3$) 1.65-1.68, 5.39, 7.28, 7.44, 7.57, 7.82, 8.39 δ.

To tert-butyl 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxylate (IX, 3.68 g) are added 40 ml of a 1/1 solution of trifluoroacetic acid and dichloromethane. After stirring for 6 hr the excess trifloroacetic acid and dichloromethane are removed under reduced pressure. Ether is added to the crude product and the solid is collected and washed again with ether. The product is dried under reduced pressure to give 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxylic acid (IX); NMR (DMSO-d_6) 1.70, 5.4, 7.59, 7.67, 8.05, 8.50, 9.39 δ.

A mixture of 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxylic acid (IX, 0.597 g) and thionyl chloride (10 ml) is stirred at reflux for 2.5 hr, whereupon it is cooled and the excess thionyl chloride is removed under reduced pressure. To the resulting solid in 25 ml of dichloromethane are added 0.541 g of 2-bromoethylamine hydrochloride, followed by 0.675 ml of triethylamine added dropwise. An ice bath is used to cool the reaction mixture as the triethylamine addition proceeds. The reaction is stirred at ice bath temperature for 20 min, then allowed to stir at 20-25° for an addtional 40 min. The mixture is then partitioned between dichloromethane and aqueous sodium bicarbonate. The organic layers are dried over sodium

sulfate and the concentrated to give N-(2-bromoethyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxamide (IX), NMR ($CDCl_3$) 1.71, 3.63, 3.95, 5.33, 7.36, 7.48, 7.62, 7.90, 8.56, 10.98 δ.

To N-(2-bromoethyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxamide (IX, 0.82 g) in THF (25 ml) and 10 ml of dichloromethane at 0° are added in a dropwise fashion potassium tert-butoxide (1M in THF, 2.2 ml). After stirring for 1 hr the solvents are removed under reduced pressure and the residue is partitioned between dichloromethane, water, and saline. The organic layers are dried over sodium sulfate and concentrated and the crude product is chromatographed on silica gel (250 ml) eluting with methanol/dichloromethane (4/96). The appropriate fractions are pooled and concentrated to give the title compound. Recrystallization from dichloromethane/ethyl acetate/hexane gives the title compound, mp 187-188°; MS (m/z) at 296; IR (mineral oil) 1673, 1508, 1307, 1029, 754 cm^{-1}; NMR ($CDCl_3$) 1.66, 4.23, 4.53, 5.49, 7.29, 7.44, 7.59, 7.83, 8.45δ.

EXAMPLE 12 5-isopropyl-4-oxo-3-(thiazol-2-yl)imidazo(1,5-a)quinoxaline (I)

A mixture of 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxylic acid (IX, EXAMPLE 11, 2.297 g) and 45 ml of thionyl chloride is stirred at reflux for 2 hr, whereupon it is cooled and the excess thionyl chloride is removed under reduced pressure. The resulting solid is stirred in 25 ml of dichloromethane cooled at 0° and 1.3 ml of triethylamine are added, followed by 1.02 ml of aminoacetaldehyde dimethyl acetal. After stirring for 1 hr, aqueous sodium bicarbonate is added to the reaction mixture and it is partitioned with dichloromethane. The organic layers are dried over sodium sulfate and concentrated. The crude product is crystallized from dichloromethane/ethyl acetate to give N-(2,2-dimethoxyethyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxamide (IX), mp 246.0-246.5°; MS (m/z) at 358; IR (mineral oil) 1663, 1356, 1593, 1633, 748 cm^{-1}; NMR ($CDCl_3$) 1.70, 3.46, 3.72, 4.64, 5.37, 7.35, 7.47, 7.61, 7.88 δ.

A mixture of N-(2,2-dimethoxyethyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxamide (1.50 g) and 1.02 g of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide are stirred at 110° in 80 ml of toluene for 1 hr, when 0.06 ml of 1,8-diazabicyclo(5.4.0)undec-7-ene are added. After 4 hr, 2 ml of dioxane are added to aid in solubility of the intermediates. The reaction is stirred at 110° for 3 days, at which time the hot mixture is filtered through a sintered glass funnel and the filtrate is concentrated under reduced pressure. The crude material is chromatographed on silica gel (250 ml) eluting with methanol/dichloromethane (4/96). The appropriate fractions are pooled and concentrated to give the title compound. The product is crystallized from dichloromethane/ethyl ether/hexane, mp 247-248°; MS (m/z) at 310; IR (mineral oil) 1649, 1392, 1293, 752, 1512, 634 cm^{-1}; NMR ($CDCl_3$) 1.69, 5.5, 7.30, 7.43, 7.46, 7.84, 8.03, 8.50. δ.

EXAMPLE 13 4,5-Dihydro-5-isopropyl-4-oxo-3-(1,2,4-triazol-3-yl) imidazo(1,5-a)quinoxaline

Step 1

A stirred suspension of 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxamide (2.5 g) and N,N-dimethylformamide dimethyl acetal (5 ml) is warmed, under nitrogen, in an oil bath from 25° to 120° during 55 min and kept at 120° for 1 hr with distillation of the methanol formed in the reaction. The reaction mixture solidified; the cooled solid is collected by filtration, washed with tert-butyl methyl ether and dried under reduced pressure to give a solid, NMR ($CDCl_3$) 1.66, 3.22, 5.33, 7.26, 7.41, 7.55, 7.82, 8.41, 8.75 δ.

Step 2

A stirred suspension of the product from Step 1 (2.75 g) in acetic acid (27.5 mol), under nitrogen, is treated with hydrazine hydrate (0.47 ml), warmed to 97° during 1 hr and kept at 97° for 1 hr 25 min. The mixture is concentrated to about one half of its original volume with a stream of nitrogen; the solid which resulted is collected by filtration and dried, under reduced pressure to give crude product. Additional product is obtained by concentrating the mother liquor and mixing the solid residue with acetic acid (1 ml) and water (0.5 ml). The combined product is recrystallized from DMF to give the title compound, NMR (DMSO-d_6) 1.61, 5.28, 7.40, 7.52, 7.85, 8.20, 8.35, 9.26δ; MS (m/z, relative intensity) 294 (M^+), 279, 252, 224, 169; IR (mineral oil) 3136, 3081, 3036, 1639, 1612, 1601 and 1588 cm^{-1}.

EXAMPLE 14 4,5-Dihydro-5-isopropyl-3-(5-methyl-1,2,4-triazol-3-yl)-4-oxoimidazo(1,5-a)quinoxaline (I)

Step 1

A stirred mixture of 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxamide (EP 0 320 136 A2, 1.0 g) and N,N-dimethylacetamide dimethyl acetal (2.5 ml) is warmed, under nitrogen, in an oil bath at 120° for 2 hr with distillation of the methanol formed in the reaction. The cooled reaction mixture is concentrated under a stream of nitrogen; the residue is dissolved in chloroform, washed with saturated sodium bicarbonate, water and saline, dried over sodium sulfate and concentrated. The residue is triturated twice with *tert*-butyl methyl ether and crystallized from methyl ethyl ketone to give the product, mp 150-152° (s, 142°); MS (m/z, relative intensity) 339 (M+), 254, 227, 212, 113; NMR ($CDCl_3$) 1.64, 2.48, 3.13, 3.22, 5.45, 7.23, 7.39, 7.55, 7.80, 8.36 δ. A second crop of product mp 142-145° (s, 130-135°) is also obtained.

Step 2

A stirred mixture of the product from Step 1 (0.66 g), acetic acid (6.5ml) and hydrazine hydrate (0.11 ml) is warmed under nitrogen from 45° to 98° during 50 min and kept at 97-98° for 4 hr. By TLC with methanol/chloroform (10/90), the mixture still contained starting

material; it is cooled, treated with one drop of hydrazine hydrate and warmed at 97° for an additional 1 hr 25min. The mixture is then concentrated under a stream of nitrogen to one half of its original volume and mixed with ice water. The solid is collected by filtration, washed with water, dried and recrystallized from methylene chloride to give the title compound, mp 268-271°; MS (m/z) 308 (M+), 293, 266, 238; IR (mineral oil) 3165, 3104, 1640, 1618, 1586 cm^{-1}; NMR ($CDCl_3$) 1.72, 2.53, 5.33, 7.35, 7.47, 7.62, 7.87, 8.56.

EXAMPLE 15 4,5-Dihydro-5-isopropyl-3-(1-methyl-1,2,4-triazol-3-yl)-4-oxoimidazo(1,5-a)quinoxaline (I)

Step 1

A stirred suspension of powdered 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxylic acid (6.22 g) in methylene chloride (180 ml), under nitrogen, at 20-25° is treated with 4 drops of dimethylformamide and then dropwise during about 15 min with a solution of oxalyl chloride (6 ml) in methylene chloride (30 ml). This mixture is stirred for 18 hr; the suspension is then concentrated under reduced pressure. The residue is suspended twice in THF with concentration after each addition. This residue is dried under reduced pressure.

Step 2

A stirred mixture of 2-methyl-3-thiosemicarbazide (2.8 g) in pyridine is cooled to -20°, under nitrogen, and treated portionwise during 20 min with the acid chloride prepared in Step 1. The mixture is kept at -30° to -20° for 1 hr, at -20° to -10° for 30 min and at 20-25° for 18 hr. It is then concentrated under reduced pressure. The residue is mixed with toluene twice with concentration after each addition. This residue is mixed with water (150 ml) and ether (20 ml) and stirred for 30 min. A stream of nitrogen is then bubbled through the mixture to remove the ether; the mixture is cooled and the solid is collected by filtration and dried under reduced pressure to give the product.

Step 3

A stirred mixture of the product from Step 2 (3.3 g) and sodium hydroxide (1M, 50 ml) is warmed to the reflux temperature during 1 hr 20 min and refluxed for an additional 20 min. The mixture is then cooled in an ice bath and acidified to pH 4-5 with hydrochloric acid (4M). The resulting solid is collected by filtration, washed with cold water and dried under reduced pressure to give a solid. This material is digested with hot chloroform (about 750 ml), the mixture is filtered and the filtrate concentrated to about 250 ml to give a solid. This process is repeated with 400 ml of hot chloroform o give additional solid. The combined solids are digested with a mixture of methanol and chloroform and filtered. The solid is dried, mp >300°; MS (m/z) 340 (M+), 298, 211; IR 3122, 3078, 3028, 1644, 1614, 1604, 1588 cm^{-1}.

Step 4

The product of Step 3 (1.3 g) is added portionwise during 10 min to nitric acid (20%, 4.2 ml) that had been warmed on a steam bath. The resulting suspension is warmed for an additional 25 min and kept at 20-25° for 1 hr. It is then cooled in an ice bath, treated with cold dilute ammonium hydroxide until the pH is 9-10 and extracted with chloroform. The extracts are washed with water and saline, dried over magnesium sulfate and concentrated. The residue is chromatographed under pressure on silica gel (200 ml) to give the product which is crystallized from methylene chloride/hexane to give the title compound, mp 243-244°. The analytical sample is recrystallized from isopropanol, mp 243-246°; MS (m/z) 308 (M+), 293, 266), 238; IR 3106, 3072, 1655, 1616, 1586 cm^{-1}; NMR ($CDCl_3$) 1.66, 4.05, 5.52, 7.27, 7.41, 7.59, 7.84, 8.21, 8.50 δ.

EXAMPLE 16 4,5-Dihydro-5-isopropyl-3-(2-methyl-1,2,4-triazol-3-yl)-4-oxoimidazo(1,5-a)quinoxaline (I)

4,5-Dihydro-5-isopropyl-4-oxo-3-(1,2,4-triazol-3-yl)-imidazo(1,5-a)quinoxaline (I, EXAMPLE 13, 1.0 g) in acetic acid (10 ml), under nitrogen, is treated with methylhydrazine (0.18 ml), warmed to 96° during 50 min and kept at 96° for 45 min. After standing at 20-25° for 18 hr, additional methylhydrazine (0.05 ml) is added and the mixture is warmed at 97° for an additional 2 hr 35 min. It is then concentrated under reduced pressure; toluene is added to the residue and the mixture is again concentrated. The residue is chromatographed on silica gel (200 ml), under pressure, eluting methanol/chloroform (3.5/96.5). The appropriate fractions are pooled and concentrated to give the product which is crystallized from methylene chloride/hexane to give the title compound, mp 230-232°; NMR ($CDCl_3$) 1.65, 4.01, 5.37, 7.33, 7.47, 7.60, 7.87, 8.07, 8.55; MS (m/z) 308 (M^+), 293, 265, 211; IR (mineral oil) 3088, 1671, 1663, 1625, 1602, 1590 cm^{-1}.

EXAMPLE 17

Following the general procedure of EXAMPLES 1-3 and making non-critical variations, the following compounds were synthesized.

a) 3-(3-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline: mp 215-217°;

b) 7-Fluoro-3-(3-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline: mp 230-231.5°;

c) 6-chloro-3-(3-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline: mp 193-193.5°;

d) 7-fluoro-4,5-dihydro-5-isopropyl-3-(4-methoxyphenyl)-4-oxoimidazo(1,5-a)quinoxaline: mp > 300° MS (EI) m/e 351, 309, 294, 239;

e) 6-chloro-4,5-dihydro-5-isopropyl-3-(4-methoxyphenyl)-4-oxoimidazo(1,5-a)quinoxaline: mp 164-165°;

f) 6-chloro-4,5-dihydro-5-isopropyl-3-(3-methoxyphenyl)-4-oxoimidazo(1,5-a)quinoxaline: mp > 300°; MS (EI) m/e 367, 325, 296;

g) 7-fluoro-4,5-dihydro-5-isopropyl-4-oxo-3-(3-trifluoromethylphenyl)imidazo(1.5-a)quinoxaline: mp 231-232°;

h) 4,5-dihydro-5-isopropyl-3-(3-methoxyphenyl)-4-oxoimidazo(1,5-a)quinoxaline: mp 180-181°;

i) 4,5-dihydro-5-isopropyl-4-oxo-3-(3-trifluoromethylphenyl)imidazo(1,5-a)quinoxaline: mp 210-211°;

j) 4,5-dihydro-5-isopropyl-3-(4-methoxyphenyl)-6-methyl-4-oxoimidazo(1,5-a)quinoxaline: mp 179-180°;

k) 3-(4-fluorophenyl)-4,5-dihydro-5-isopropyl-6-methyl-4-oxoimidazo(1,5-a)quinoxaline: mp 165-166°.

EXAMPLE 18 3-(4-Cyclopropylthiazol-2-yl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline

A mixture of 3.02 g of 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxamide (as prepared in Example 14) and 3.39 g of 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent) in 60 mL of THF is stirred at reflux. After 1.5 hours an additional 1 g of Lawesson's reagent is added, and 2.5 hours later another 1g of Lawesson's reagent is added. After 2.25 hours additional stirring at reflux, the reaction mixture is cooled and the solvent is removed under reduced pressure. The residue is chromatographed on silica gel using a gradient solvent system of 4% to 10% methanol--dichloromethane. The fractions containing 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-thiocarboxamide are rechromatographed on silica gel using 4% methanol--96% dichloromethane containing about 0.1% of ammonium hydroxide to give 2.25 g of 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-thiocarboxamide. To 0.675 g of this material is added 0.46 g of 1-(bromomethyl)cyclopropyl ketone and 15 mL of ethanol. After stirring for 3.3 hours an additional 0.15 g of 1-(bromomethyl)cyclopropyl ketone is added and the reaction mixture is stirred overnight. The ethanol is then removed under reduced pressure and dichloromethane is added, followed by a small amount of hexane. The material which crystallizes out is the unstable hydrobromide salt of the title compound. Recombination of the solid and filtrate, followed by partitioning between dichloromethane and aq. sodium bicarbonate, drying of the organic layers over sodium sulfate, concentration, and recrystallization from methanol--dichloromethane-hexane gives 0.43 g of the subject compound, 3-(4-cyclopropylthiazol-2-yl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline, as a yellow solid, m.p. 235.5-237 °C.

EXAMPLE 19 3-(4-Cyclopropyloxazol-2-yl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline

A mixture of 0.617 g of 4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxylic acid (as prepared in Example 11) and 10 mL of thionyl chloride is stirred at reflux for 1.25 hours and then cooled. The excess thionyl chloride is then removed under reduced pressure and dichloromethane is added to the residue. The dichloromethane is then removed from the mixture under reduced pressure. To the residue is added 0.339 g of aminomethylcyclopropyl ketone hydrochloride, 0.70 mL of triethylamine, and 20 mL of dichloromethane. After stirring for 1.25 hours, the reaction mixture is partitioned between dichloromethane, aq. sodium bicarbonate, 1N aq. HCl, and aq. sodium bicarbonate. The organic layers are dried over sodium sulfate and concentrated. The residue is chromatographed on silica gel using 8% methanol--92% dichloromethane as eluent to give 0.672 g of product, of which 0.64 g is stirred with 1.1 g of phosphorus oxychloride and 30 mL of toluene at 110 °C for 4.3 hrs. The reaction mixture is then poured onto ice/water and extracted with dichloromethane. The organic layers are backwashed with aq. sodium bicarbonate and then dried over sodium sulfate and concentrated. The residue is chromatographed on silica gel using 4% methanol--96% dichloromethane as eluent to give 0.589 g of product, which was crystallized from dichloromethane/hexane to give 0.448 g of the subject compound, 3-(4-cyclopropyloxazol-2-yl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline, m.p. 211-212 °C.

EXAMPLE 20 3-(4-Cyclopropyloxazol-2-yl)-7-fluoro-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline

Using the procedure for 3-(4-cyclopropyloxazol-2-yl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline (EXAMPLE 19), but starting with 7-fluoro-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline-3-carboxylic acid, 0.411 g of the subject compound was prepared, m.p. 261-262 °C.

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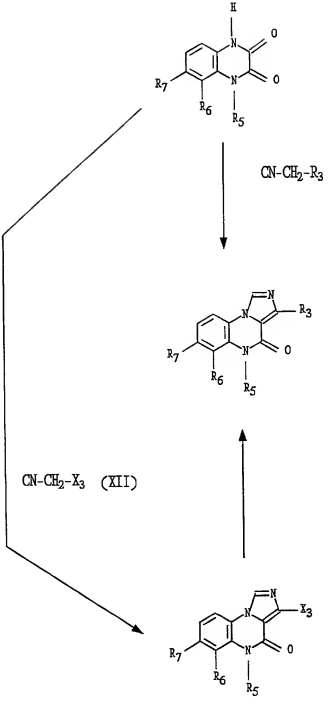

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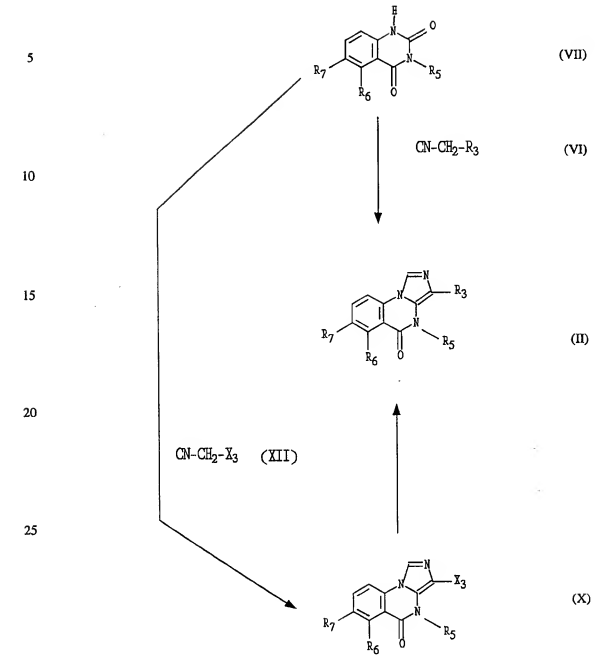

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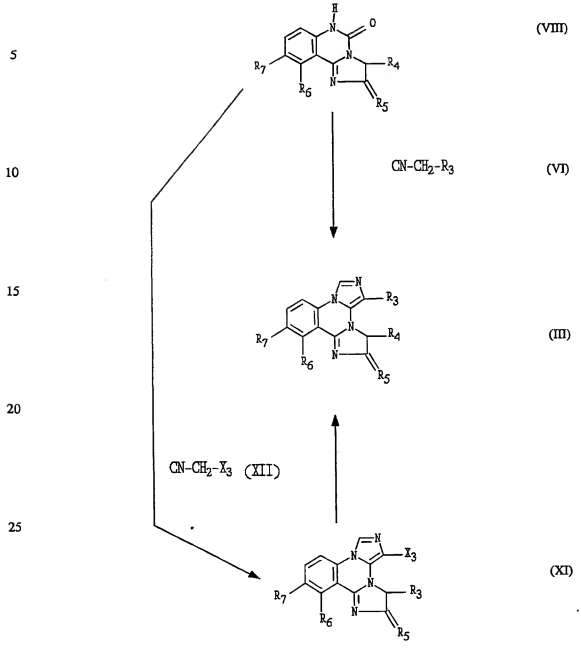

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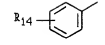

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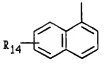

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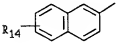

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(Aryl-IV)

(Aryl-V)

(Aryl-VI)

(Aryl-VII)

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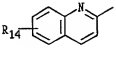
(Aryl-X)

(Aryl-XI)

(Aryl-XII)



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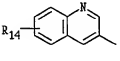

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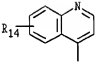
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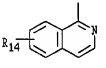
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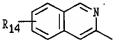
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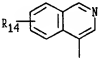
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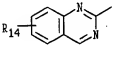
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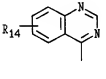
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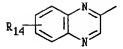

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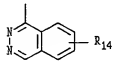

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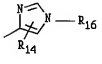

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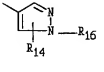

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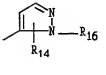

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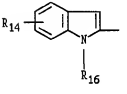
(Aryl-XXXI)



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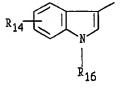
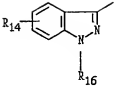


(Aryl-XXXIII)

CHART D - Continued



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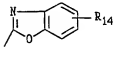
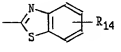


(Aryl-XXXV)



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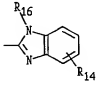

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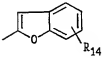

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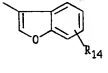

(Aryl-XXXIX)

(Aryl-XL)

CHART D - Continued


(Aryl-XLI)


(Aryl-XLII)


(Aryl-XLIII)


(Aryl-XLIV)


(Aryl-XLV)

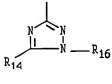
(Aryl-XLVI)

CHART D - Continued

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(Aryl-XLVIII)

(Aryl-XLIX)

(Aryl-L)

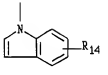
(Aryl-LI)

(Aryl-LII)

(Aryl-LIII)

CHART D - Continued

(Aryl-LIV)



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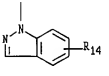

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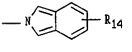

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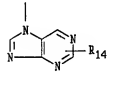


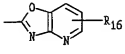
(Aryl-LVIII)

(Aryl-LIX)

(Aryl-LX)

CHART D - Continued

(Aryl-LXI)



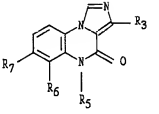
(Aryl-LXII)

(Aryl-LXIII)

(Aryl-LXIV)

WHAT IS CLAIMED:

1. A 4-oxoimidazo(1,5-a)quinoxaline of formula (I)



(I)

or a pharmaceutically acceptable salt thereof,

wherein R_3 is

—Aryl —COAryl —CSR_{11}

(a) (b) (c) (d)

wherein "Aryl" is as defined in Chart D and is substituted with R_{14} and R_{16} as indicated;

R_5 is C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, C_{2-6} alkenyl (optionally substituted with C_{1-3} alkyl), $(CH_2)_n$-Aryl, $(CH_2)_mN(R_{12})_2$, or $(CH_2)_mOR_{11}$ and n is 0-4 and m is 2-4;

R_6 and R_7 are independently H, F, Cl, Br, I, C_1-C_4 alkyl, C≡N, NO_2, CF_3, $(CH_2)_nOR_{11}$, CO_2R_{11}, $CON(R_{12})_2$, $(CH_2)_nN(R_{12})_2$, $(OCH_2CH_2)_n$-OH or $NHCOR_{11}$;

R_8 is O, S, NH, NCH_3, $N(CH_2)_n$-C_{3-7} cycloalkyl, -$C(R_9)_2$ or NCHO;

R_9 is H, C_{1-4} alkyl, phenyl (except that only one R_9 can be phenyl or t-butyl at the same time);

R_{11} is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, or -$(CH_2)_n$-Aryl;

R_{12} is independently H, C_{1-6} alkyl, C_3-C_7 cycloalkyl, -C_{1-4} alkyl-C_{3-7} cycloalkyl, phenyl, or taken together with the attached nitrogen atom to form a heterocyclic ring -$N^*(CH_2)_pR_{13}(CH_2)_o$* where the * indicates the atoms bonded to each other to form said heterocyclic ring, where p is 2-5 and o is 0-3;

R_{13} is O, S, CO, CH_2, NR_{16};

R_{14} is independently H, F, Cl, Br, I, CN, NO_2, $OCOR_{11}$, $(CH_2)_nCF_3$, C_{1-6} alkyl, C_3-C_7 cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, $(CH_2)_nN(R_{12})_2$, $(CH_2)_nOR_{11}$, $N(R_{12})COR_{11}$, $(CH_2)_nCO_2R_{11}$, $(CH_2)_nSR_{11}$, $SO_2N(R_{12})_2$, COR_{11}, phenyl (optionally substituted with F, Cl, Br, OCH_3, CH_3 or CF_3); and

R_{16} is H, C_{1-4} alkyl, C_3-C_7 cycloalkyl, CHO, C_{1-4} alkyl-C_{3-7} cycloalkyl, CO-R_{11}.

R_{16} is H, C_{1-4} alkyl, C_3-C_7 cycloalkyl, CHO, C_{1-4} alkyl-C_{3-7} cycloalkyl, CO-R_{11}.

2. A 4-oxoimidazo(1,5-a)quinoxaline (I) according to claim 1 where R_3 is selected from the group consisting of benzoxazol-2-yl, thiazol-2-yl, oxazolin-2-yl, 1,2,4-triazol-3-yl and a phenyl optionally substituted with one $-CH_3$, $-OCH_3$ or -F.

3. A 4-oxoimidazo(1,5-a)quinoxaline (I) according to claim 1 where R_3 is selected from the group consisting of 4-fluorophenyl, thiazol-2-yl and benzoxazol-2-yl.

4. A 4-oxoimidazo(1,5-a)quinoxaline (I) according to claim 1 where R_5 is C_1-C_4 alkyl.

5. A 4-oxoimidazo(1,5-a)quinoxaline (I) according to claim 1 where R_6 and R_7 are independently -H, -F, -Cl, $-CF_3$ or $-CH_3$.

6. A 4-oxoimidazo(1,5-a)quinoxaline (I) according to claim 1 where the 4-oxoimidazo (1,5-a)quinoxaline (I) is

a) 4,5-dihydro-5-isopropyl-3-(4-methoxyphenyl)-4-oxoimidazo(1,5-a)quinoxaline,
b) 7-fluoro-4,5-dihydro-5-isopropyl-4-oxo-3-phenylimidazo(1,5-a)quinoxaline,
c) 3-(4-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline,
d) 7-fluoro-3-(4-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline,
e) 6-chloro-3-(fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline,
f) 4,5-dihydro-5-isopropyl-4-oxo-3-phenylimidazo(1,5-a)quinoxaline,
g) 3-(2-furyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline,
h) 4,5-dihydro-5-isopropyl-3-(4-methylphenyl)-4-oxoimidazo(1,5-a)quinoxaline,
i) 3-(benzoxazol-2-yl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline,
j) 3-(benzoxazol-2-yl)-7-fluoro-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline,
k) 4,5-dihydro-5-isopropyl-3-(oxazolin-2-yl)-4-oxoimidazo(1,5-a)quinoxaline,
l) 4,5-dihydro-5-isopropyl-4-oxo-3-(thiazol-2-yl)imidazo(1,5-a)quinoxaline,
m) 4,5-dihydro-5-isopropyl-4-oxo-3-(1,2,4-triazol-3-yl)imidazo(1,5-a)quinoxaline,
n) 4,5-dihydro-5-isopropyl-3-(5-methyl-1,2,4-triazol-3-yl)-4-oxoimidazo(1,5-a)quinoxaline,
o) 4,5-dihydro-5-isopropyl-3-(i-methyl-1,2,4-triazol-3-yl)-4-oxoimidazo(1,5-a)quinoxaline,
p) 4,5-dihydro-5-isopropyl-3-(2-methyl-1,2,4-triazol-3-yl)-4-oxoimidazo(1,5-a)quinoxaline,
q) 3-(3-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline,
r) 7-Fluoro-3-(3-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline,
s) 6-chloro-3-(3-fluorophenyl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline,
t) 7-fluoro-4,5-dihydro-5-isopropyl-3-(4-methoxyphenyl)-4-oxoimidazo(1.5-a)quinoxaline,

u) 6-chloro-4,5-dihydro-5-isopropyl-3-(4-methoxyphenyl)-4-oxoimidazo(1,5-a)quinoxaline,

v) 6-chloro-4,5-dihydro-5-isopropyl-3-(3-methoxyphenyl)-4-oxoimidazo(1,5-a)quinoxaline,

w) 7-fluoro-4,5-dihydro-5-isopropyl-4-oxo-3-(3-trifluoromethylphenyl)imidazo (1,5-a)quinoxaline,

x) 4,5-dihydro-5-isopropyl-3-(3-methoxyphenyl)-4-oxoimidazo(1,5-a)quinoxaline,

y) 4,5-dihydro-5-isopropyl-4-oxo-3-(3-trifluoromethylphenyl)imidazo(1,5-a)quinoxaline,

z) 4,5-dihydro-5-isopropyl-3-(4-methoxyphenyl)-6-methyl-4-oxoimidazo(1,5-a)quinoxaline,

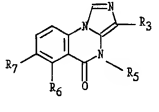
aa) 3-(4-fluorophenyl)-4,5-dihydro-5-isopropyl-6-methyl-4-oxoimidazo(1,5-a)quinoxaline,

bb) 3-(4-Cyclopropylthiazol-2-yl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline,

cc) 3-(4-Cyclopropyloxazol-2-yl)-4,5-dihydro-5-isopropyl-4-oxoimidazo(1,5-a)quinoxaline, or

dd) 3-(4-Cyclopropyloxazol-2-yl)-7-fluoro-4,5-dihydro-5-isopropyl-4-oxoimidazo (1,5-a)quinoxaline.

7. A 5-oxoimidazo(1,5-a)quinazoline of formula (II)



(II)

or a pharmaceutically acceptable salt thereof,

wherein R_3 is

(a)

(b)

(c)

(d)

wherein "Aryl" is as defined in Chart D and is substituted with R_{14} and R_{16} as indicated;

R_5 is C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, C_{2-6} alkenyl (optionally substituted with C_{1-3} alkyl), $(CH_2)_n$-Aryl, $(CH_2)_mN(R_{12})_2$, or $(CH_2)_mOR_{11}$ and n is 0-4 and m is 2-4;

R_6 and R_7 are independently H, F, Cl, Br, I, C_1-C_4 alkyl, C≡N, NO_2, CF_3, $(CH_2)_nOR_{11}$, CO_2R_{11}, $CON(R_{12})_2$, $(CH_2)_nN(R_{12})_2$, $(OCH_2CH_2)_n$-OH or $NHCOR_{11}$;

R_8 is O, S, NH, NCH_3, $N(CH_2)_n$-C_{3-7} cycloalkyl, -$C(R_9)_2$ or NCHO;

R_9 is H, C_{1-4} alkyl, phenyl (except that only one R_9 can be phenyl or t-butyl at the same time);

R_{11} is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, or -$(CH_2)_n$-Aryl;

R_{12} is independently H, C_{1-6} alkyl, C_3-C_7 cycloalkyl, -C_{1-4} alkyl-C_{3-7} cycloalkyl, phenyl, or taken together with the attached nitrogen atom to form a heterocyclic ring -N*$(CH_2)_pR_{13}$ $(CH_2)_o$* where the * indicates the atoms bonded to each other to form said heterocyclic ring, where p is 2-5 and o is 0-3;

R_{13} is O, S, CO, CH_2, NR_{16};

R_{14} is independently H, F, Cl, Br, I, CN, NO_2, $OCOR_{11}$, $(CH_2)_nCF_3$, C_{1-6} alkyl, C_3-C_7 cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, $(CH_2)_nN(R_{12})_2$, $(CH_2)_nOR_{11}$, $N(R_{12})COR_{11}$, $(CH_2)_nCO_2R_{11}$, $(CH_2)_nSR_{11}$, $SO_2N(R_{12})_2$, COR_{11}, phenyl (optionally substituted with F, Cl, Br, OCH_3, CH_3 or CF_3); and

R_{16} is H, C_{1-4} alkyl, C_3-C_7 cycloalkyl, CHO, C_{1-4} alkyl-C_{3-7} cycloalkyl, CO-R_{11}.

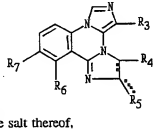
8. A 5-oxoimidazol(1,5-a)quinazoline (II) according to claim 7 where R_3 is selected from the group consisting of substituted phenyl, benzoxazol-2-yl, thiazol-2-yl, oxazolin-2-yl and 1,2,4-triazol-3-yl.

9. A 5-oxoimidazol(1,5-a)quinazoline (II) according to claim 7 where R_3 is selected from the group consisting of 4-fluorophenyl, thiazol-2-yl and benzoxazol-2-yl.

10. A 5-oxoimidazol(1,5-a)quinazoline (II) according to claim 7 where R_5 is C_1-C_4 alkyl.

11. A 5-oxoimidazol(1,5-a)quinazoline (II) according to claim 7 where R_6 and R_7 are independently -H, -F, -Cl, -CF_3 or CH_3.

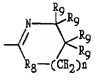
12. A diimidazoquinazoline of formula (III)



(III)

or a pharmaceutically acceptable salt thereof.

wherein R_3 is



—Aryl —COAryl —CSR_{11}

(a) (b) (c) (d)

wherein "Aryl" is as defined in Chart D and is substituted with R_{14} and R_{16} as indicated;

R_4 is H, or C_1-C_6 alkyl;

R_5 is H, C_{1-8} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, C_{2-6} alkenyl (optionally substituted with C_{1-3} alkyl), $(CH_2)_n$-Aryl, $(CH_2)_mN(R_{12})_2$, or $(CH_2)_mOR_{11}$ and n is 0-4 and m is 2-4;

R_6 and R_7 are independently H, F, Cl, Br, I, C_1-C_4 alkyl, C≡N, NO_2, CF_3, $(CH_2)_nOR_{11}$, CO_2R_{11}, $CON(R_{12})_2$, $(CH_2)_nN(R_{12})_2$, $(OCH_2CH_2)_n$-OH or $NHCOR_{11}$;

R_8 is O, S, NH, NCH_3, $N(CH_2)_n$-C_{3-7} cycloalkyl, -$C(R_9)_2$ or NCHO;

R_9 is H, C_{1-4} alkyl, phenyl (except that only one R_9 can be phenyl or t-butyl at the same time);

R_{11} is H, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, or -$(CH_2)_n$-Aryl;

R_{12} is independently H, C_{1-6} alkyl, C_3-C_7 cycloalkyl, -C_{1-4} alkyl-C_{3-7} cycloalkyl, phenyl, or taken together with the attached nitrogen atom to form a heterocyclic ring -N*$(CH_2)_pR_{13}(CH_2)_o$* where the * indicates the atoms bonded to each other to form said heterocyclic ring, where p is 2-5 and o is 0-3;

R_{13} is O, S, CO, CH_2, NR_{16};

R_{14} is independently H, F, Cl, Br, I, CN, NO_2, $OCOR_{11}$, $(CH_2)_nCF_3$, C_{1-6} alkyl, C_3-C_7 cycloalkyl, C_{1-4} alkyl-C_{3-7} cycloalkyl, $(CH_2)_nN(R_{12})_2$, $(CH_2)_nOR_{11}$, $N(R_{12})COR_{11}$, $(CH_2)_nCO_2R_{11}$, $(CH_2)_nSR_{11}$, $SO_2N(R_{12})_2$, COR_{11}, phenyl (optionally substituted with F, Cl, Br, OCH_3, CH_3 or CF_3); and

R_{16} is H, C_{1-4} alkyl, C_3-C_7 cycloalkyl, CHO, C_{1-4} alkyl-C_{3-7} cycloalkyl, CO-R_{11}.

13. A diimidazoquinazoline (III) according to claim 12 where R_3 is selected from the group consisting of substituted phenyl, benzoxazol-2-yl, thiazol-2-yl, oxazolin-2-yl and 1,2,4-triazol-3-yl.

14. A diimidazoquinazoline (III) according to claim 12 where R_3 is selected from the group consisting of 4-fluorophenyl, thiazol-2-yl and benzoxazol-2-yl.

15. A diimidazoquinazoline (III) according to claim 12 where R_5 is H or C_1-C_4 alkyl.

16. A diimidazoquinazoline (III) according to claim 12 where R_6 and R_7 are independently -H, -F, -Cl, $-CF_3$ or CH_3.

17. A use of a compound of Formula I, II or III for the preparation of a medicament useful for treating central nervous system disorders associated with the benzodiazepine receptors in a patient in need of such treatment comprising administering to the patient a therapeutically-effective amount of a compound of Formula I, II or III for alleviation of such disorder.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/00291

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D487/04; C07D487/14; A61K31/495; //(C07D487/04, 241:00,235:00)(C07D487/04,239:00,235:00)(C07D487/14, 239:00,235:00, 235:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 283 162 (FERROSAN) 21 September 1988 cited in the application see claims 1,7	1,7,17
X	see example 12b	7
A	WO,A,9 107 407 (NOVO NORDISK) 30 May 1991 cited in the application see claims 1,5	1,17
A	EP,A,0 417 027 (FERROSAN) 13 March 1991 see claims 1,7	12,17

* Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
27 APRIL 1993	13. 05. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALFARO FAUS I.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9300291
SA 69292

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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